Correspondence

Malnutrition and Variability in CD4+ Cell Counts in African Populations

To the Editor—Williams et al. [1] investigated a mathematical model to predict the distribution of $CD4^+$ cell counts among HIV-positive adults by use of the distribution among HIV-negative adults in African populations. The study was mainly based on data collected in South Africa and Zambia. The authors noted that $CD4^+$ cell counts vary widely within and among populations. The $CD4^+$ cell count distributions among HIV-negative people had a higher mean in South Africa than in Zambia, but the mean rate of decrease in $CD4^+$ cell count among HIV-positive people was higher in South Africa, and mean survival was shorter in South Africa than in Zambia at a given $CD4^+$ cell count. The authors did not provide an explanation for these observations, which are important for the prediction of mortality at a given $CD4^+$ cell count. Predictions of disease progression and mortality inform the decision-making process about the commencement of antiretroviral treatment in an individual HIV-infected patient.

The authors' findings could be explained by the impact of nutritional status on $CD4^+$ cell counts. In malnutrition, the thymus gland undergoes severe atrophy due to apoptosis-induced thymocyte depletion, particularly affecting the immature $CD4^+$ cells, as well as a decrease in cell proliferation [2]. This process has been linked to decreased leptin and increased glucocorticoid levels in malnutrition [3]. $CD4^+$ cell counts were found to be lower in children with nonedematous malnutrition than in those with edematous malnutrition [4]. The population in Zambia at the time the studies the authors referred to were conducted had a significantly higher proportion of malnourished people than did the population in South Africa, where the economic conditions started to improve with increased rates of obesity [5, 6]. This may explain the lower mean $CD4^+$ cell count among HIV-negative people in the Zambian study. It is unlikely that the lower mean $CD4^+$ cell count in Zambia was due to an increased burden of other infectious diseases, because increased cytokine levels due to ongoing infections would (for example via tumor necrosis factor and NF-κB–mediated long terminal repeat–driven increased HIV transcription) have led to accelerated disease progression and increased mortality due to HIV infection. Malnutrition rather than increased infectious-disease burden is, therefore, also the most likely explanation for the finding of a study in Ethiopia in which, at lower $CD4^+$ cell counts, life expectancy in HIV-positive patients was similar to that in The Netherlands [6]. Low $CD4^+$ cell counts due to malnutrition are associated with a more functional immune system than are low $CD4^+$ cell counts due to HIV-induced T cell apoptosis, and many immune functions are well preserved in people with malnutrition [7]. Future mathematical models predicting disease progression and mortality in HIV-positive populations need to relate $CD4^+$ cell counts to body mass index.

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Reply to Eisenhut

To the Editor—Eisenhut [1] discusses the role of malnutrition as a determinant of $CD4^+$ cell counts, especially in Africa. It is known that genetic, immunological, physiological, and behavioral factors are associated with $CD4^+$ cell counts within and among populations, and we referred to some of these factors in our article [2]. However, our intention was not to explain the reasons for this variation but, rather, to investigate the more limited question of the relationship between the distributions of $CD4^+$ cell counts among HIV-positive and HIV-negative people from the same population. The surprising conclusion was that, in populations in which the initial mean $CD4^+$ cell count is low, the

rate of decline in $CD4^+$ cell counts is correspondingly low, so that the time to AIDS and death is not substantially affected.

Eisenhut suggests that $CD4^+$ cell counts were lower in the Zambian population than in the South African population because the Zambians were malnourished, and he suggests that malnutrition may not result in a significant deterioration in immune function, even if it leads to a reduction in $CD4^+$ cell counts. He suggests that, taken together, these factors may explain the similar time to death in the 2 populations. To this interesting suggestion, we must reply "perhaps."

First, without comparative measurements of nutritional status, it is not certain that the Zambians were less well nourished than the South Africans. Nutritional status was, however, measured in the Zambian study, and people with opportunistic infections, but not asymptomatic HIV infection, showed signs of malnourishment [3]; however, malnutrition could have been the cause or the effect of the opportunistic infections [4]. Second, there is uncertainty about the role of malnutrition in lowering $CD4^+$ cell counts [5] and leading to functional impairment of the immune system [5, 6].

If the nutritional statuses of the 2 populations were indeed different, and if malnutrition reduces $CD4^+$ cell counts but also leads to a functional deterioration in the immune system [4], we might have expected a more rapid progression to AIDS and death among the Zambians, compared with that among the South Africans. This appears not to be the case. The putative explanation for this is that, since $CD4^+$ cells are prime targets for HIV, the lack of $CD4^+$ cells in Zambians as compared with South Africans limits the ability of the virus to replicate, and this balances out the effect of malnutrition on disease progression and, therefore, survival.

We believe that these questions still demand answers, especially in view of the fact that $CD4^+$ cell counts are widely used as part of the algorithm for deciding when to start antiretroviral therapy. Better data on the determinants of $CD4^+$ cell counts, together with more extensive data on time trends in $CD4^+$ cell counts and survival, might help us to develop better predictive models of the outcome of HIV infections. This, in turn, could help to bridge the gap between what is happening at the cellular level and what is happening at the population level, with important implications for the control of HIV/AIDS. The possibilities for doing such work are now limited, since it is essential that HIV-positive people have access to antiretroviral therapy. However, sufficient historical data must have been collected over the past 25 years in the Multi-centre AIDS Cohort Study (MACS), the Concerted Action on Sero-Conversion to AIDS and Death in Europe (CASCADE) Collaboration, and other such studies to help resolve these questions.

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